RESEARCH HIGHLIGHT

Pituitary adenomas: new insights, new therapeutic targets

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The genomic and transcriptomic landscape of pituitary adenomas has not been adequately elucidated. In a landmark study published in *Cell Research*, Zhang et al. analyzed multi-omics data from a large number of pituitary adenomas to characterize the molecular landscape of these tumors, yielding new mechanistic insights and identifying potential therapeutic targets.

Pituitary adenomas (pituitary neuroendocrine tumors or PitNETs) are monoclonal neoplasms that represent the large majority of sellar masses.[1,2] Surgery has been the mainstay of treatment for most pituitary adenomas with the exception of prolactinomas. There is a paucity of molecular targets that have been fruitfully exploited to date, including dopamine receptors and somatostatin receptors, reflecting limitations in our understanding of the molecular underpinnings of these tumors.

Several factors have hindered previous efforts at elucidating the pathogenesis of pituitary adenomas, including the small size of many of these tumors, possible admixture of tumor cells with normal pituitary tissue in specimens and tumor genetic heterogeneity. In addition, available animal models of pituitary adenomas may not accurately recapitulate the biologic behavior of these tumors in humans.[3]

About 95% of pituitary adenomas are sporadic with no evident hereditary/familial contribution to their pathogenesis.[1] Previous studies have reported that the tumor mutational burden of pituitary adenomas is generally low.[1,4] Recurrent somatic mutations appear to occur in a relatively small number of genes, including activating mutations in *GNAS* in ~40% of somatotroph adenomas and *USP8* in ~35% of corticotroph adenomas.[1] Copy number alterations have been commonly reported in pituitary adenomas.[5] In addition, alterations in DNA methylation profiles, including promoter hypomethylation, have been observed and may drive growth hormone (GH) and pro-opiomelanocortin (POMC) expression in somatotroph and corticotroph tumors, respectively.[6] Downregulation of tumor suppressors (such as p16, Rb and MEG3) and overexpression of cyclin D1 and PTTG are common in pituitary adenomas and may occur via epigenetic mechanisms, thereby driving unrestrained cell growth.[4] Defects in receptor signaling, activation of senescence mechanisms and atypical microRNA expression profiles have also been implicated in the pathogenesis of pituitary adenomas.[2,4] In addition, investigation of the tumor microenvironment in pituitary adenomas represents another promising research avenue.[7]

In a landmark study recently published in *Cell Research*, Zhang et al. compiled and characterized an extensive dataset obtained through multi-omics (genomics, transcriptomics, proteomics and phosphoproteomics) analyses of specimens from 200 pituitary adenomas of diverse histologic subtypes and 7 anterior pituitary glands (used as controls), and went on to validate their major findings in a separate cohort of 750 tumors.[8]

The investigators reported *GNAS* copy number gain among tumors of the PIT1 lineage. Such GNAS copy number gains were associated with upregulation in cell cycle and DNA replication pathways, suggesting that these may be driving cell proliferation and raising the possibility that inhibition of these pathways may be efficacious in restraining tumor growth. Using proteomics, they identified 7 tumor clusters, including a cluster (primarily among PIT1 lineage tumors) characterized by upregulation of epithelial-mesenchymal transition (EMT) markers and increased tumor invasiveness. These data suggest that targeting this pathway may be therapeutically beneficial for patients with such locally invasive tumors.

The investigators identified upregulation of the epidermal growth factor receptor (EGFR) in tumors of TPIT (corticotroph) lineage, and reported EGFR T693 phosphorylation in silent TPIT tumors. They also identified 4 transcription factors that were upregulated in tumors of TPIT lineage and might be promoting POMC biosynthesis. These data suggest potential therapeutic targets in TPIT positive tumors. Additionally, hypoxia and VEGF signaling pathways were found to be upregulated in tumors of SF1 (gonadotroph) and NULL lineages, suggesting that inhibitors of these pathways might serve as therapeutic targets for these tumors.

The researchers additionally characterized the immune infiltration patterns in the tumor microenvironment and distinguished 4 distinct tumor clusters characterized by distinct patterns of immune and stromal features, including CTLA4 or PDL1 upregulation in some of these clusters, suggesting that the corresponding tumors might be amenable to immunotherapy with immune checkpoint inhibitors.

In aggregate, this study represents a tour-de-force effort at characterizing the molecular landscape of these tumors and identifying novel treatment targets.[8] These findings open new avenues for investigation. Mechanistic studies will be helpful to further characterize pathways driving tumor growth in distinct tumor subtypes; prospective studies will be needed to confirm the role of these biomarkers, such as EMT markers, in predicting pituitary tumor behavior (invasiveness, aggressiveness, metastases); and inhibitors of pathways identified in the study will undoubtedly be tested in vitro and, ultimately, in vivo, as potential therapies for patients with these tumors.

REFERENCES

1. Vandeva, S., Daly, A. F., Petrossians, P., Zacharieva, S. & Beckers, A. *Eur. J. Endocrinol.* **181**, R235–R254 (2019).

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2. Melmed, S. et al. *Endocr. Rev.* **43**, 1003–1037 (2022).
3. Cano, D. A., Soto-Moreno, A. & Leal-Cerro, A. *Front. Oncol.* **4**, 203 (2014).
4. Srirangam Nadhamuni, V. & Korbonits, M. *Endocr. Rev.* **41**, 821–846 (2020).
5. Bi, W. L. et al. *Clin. Cancer Res.* **23**, 1841–1851 (2017).
6. Salomon, M. P. et al. *Clin. Cancer Res.* **24**, 4126–4136 (2018).
7. Ilie, M. D., Vasiljevic, A., Bertolino, P. & Raverot, G. *Endocr. Rev.* https://doi.org/10.1210/endrev/bnac024 (2022).
8. Zhang, F. et al. *Cell Res.* **32**, 1047–1067 (2022).

ADDITIONAL INFORMATION

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